ABSTRACT & COMMENTARY

Preventing Pertussis: Are Your Patients and Their Families ‘Cocooning’?

By Rebecca H. Allen, MD, MPH

Assistant Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI

Dr. Allen reports she is a consultant for Bayer.

SYNOPSIS: Prior vaccination of both parents with Tdap ("cocooning") protects newborn infants from contracting pertussis.


In March 2009, amidst a pertussis epidemic, the Australian state of New South Wales initiated a Tdap (tetanus-diphtheria-acellular pertussis) vaccination program free of charge for mothers, fathers, grandparents, and other close adult contacts of infants aged < 12 months. To evaluate the program, researchers conducted a case-control study of 217 infants with pertussis and 585 randomly sampled controls matched by date of birth (± 7 days) and “statistical subdivision,” defined as socially and economically homogeneous regions in the state. Cases, collected between April 2009 and March 2011, included infants < 4 months of age with either definitive laboratory evidence (culture or nucleic acid testing) of pertussis or suggestive laboratory evidence (serology) together with a compatible clinical illness (coughing illness lasting 2 weeks associated with paroxysms, inspiratory whoop, or post-tussive vomiting). All cases of pertussis in New South Wales are required to be reported to the Ministry of Health. Parents of cases and controls were interviewed by telephone to ascertain infant history such as breastfeeding, daycare attendance, and vaccination history. All household contacts were identified and the vaccination history of adults was obtained by self report and then confirmed with clinic records when possible (16% of sample). Vaccination status of cases, controls, and siblings was confirmed through the Australian Childhood Immunization Register.

Compared with control households, case households...
had lower education and income levels, mothers were less likely to have breastfed for more than 2 weeks, and they were more likely to include at least one other child in the home. Overall, similar proportions of mothers reported receiving the Tdap vaccine at any time (76% cases vs 79% controls). However, fewer mothers of the cases had been vaccinated either before pregnancy or after birth but ≥ 4 weeks before the onset of the disease (22% cases vs 32% controls). Case fathers were also less likely to report receiving Tdap at least 4 weeks before the onset of disease (20% cases vs 31% controls). In multivariable analysis, after adjusting for income, education, and number and age of siblings, the protective effect of vaccinating both parents (compared with vaccinating neither) for preventing infant pertussis was 51% (95% confidence interval, 10%-73%). In this analysis, immunizing just the mother or father alone did not result in a statistically significant protective effect.

**COMMENTARY**

The incidence of pertussis in the United States has been rising with 48,000 cases reported in 2012 and 20 deaths, 15 of which occurred in infants < 3 months of age. Indeed, most severe pertussis infections occur in this age group. Given that infants cannot receive the vaccine against diphtheria, tetanus, and pertussis until 2 months of age, they are vulnerable to pertussis after birth. Studies show that newborns often contract pertussis from household contacts, with parents being the source in 50-55% of young infant cases, grandparents in 6-8%, and siblings in up to 20%. In 2006, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended a strategy to prevent neonatal pertussis infection called “cocooning.” This approach, Tdap was administered to all women in the immediate postpartum period and all other family members and caregivers (who had not received the vaccine) at least 2 weeks before infant contact in order to surround the newborn with a protective “cocoon.”

In this study in *Pediatrics* provides some of the first field evidence that this approach, if actually implemented, does protect newborns from the disease. While this study has limitations, especially regarding verification of the timing of adult vaccination, it has an adequate sample size and methodology. In the years after the study period, however, ACIP modified its recommendations to state that women who had not previously received a dose of Tdap should be vaccinated during pregnancy, ideally after 20 weeks of gestation. If it was not given during pregnancy, then mothers should still be immunized in the immediate postpartum period and “cocooning” should also be performed. This change was due to challenges in reaching all the adult contacts for vaccination given our fragmented health care system and uptake of the vaccine postpartum was not very high. Unfortunately, pertussis cases persisted in the United States and ACIP recently changed its recommendations again in 2013. With knowledge of the proven safety of adult Tdap vaccination and the fact that immunity does wane significantly after immunization, ACIP now recommends that women receive a dose of Tdap during each pregnancy, irrespective of their prior history. Ideally, Tdap should be given between 27 and 36 weeks so that the maternal antibody response and passive antibody transfer to the newborn are maximized. ACIP also reiterated that “cocooning” should still be practiced for the other adults who would have contact with the newborn. Nevertheless, a cost-effectiveness analysis has recently shown that vaccination during each pregnancy is the superior strategy for averting infant pertussis, even more than postpartum vaccination plus “cocooning.”

While obstetrician-gynecologists do not care for newborns with pertussis, we have an important role to play in preventing the disease. For various reasons, pertussis has resurfaced in the United States and the world but one main reason is the lower efficacy of acellular vaccines compared to past whole-cell vaccines and the waning immunity after acellular vaccines. In fact, it is estimated that vaccine effectiveness lasts only about 2 years after injection. When I first heard the latest recommendations that we need to vaccinate women during every single pregnancy, I was surprised and thought the strategy was overly aggressive. Now, however, I see the logic behind the approach given that pregnant women have access to medical care and vaccinations, immunity wanes rapidly, and this is a sure way to provide protection to infants prior to their own 2-month diphtheria, tetanus, and pertussis vaccination. Although I still
think “cocooning” should be encouraged, it is difficult to coordinate a vaccination campaign for an entire family given that each member likely has his or her own medical provider. While this Australian study occurred in the context of free Tdap vaccines for all adults, those types of campaigns are not seen often in the United States. For more information about this issue, the American College of Obstetricians and Gynecologists runs an informative website, www.immunizationforwomen.org.

REFERENCES

ABSTRACT & COMMENTARY

Does Single or Double Insemination During Ovulation Induction Cycle Increase Pregnancy Rates?

By Michael A. Thomas, MD

Professor, Fellowship and Division Director, Section of Reproductive Endocrinology and Infertility, University of Cincinnati Academic Health Center

Dr. Thomas reports no financial relationships relevant to this field of study.

SYNOPSIS: Performing intrauterine insemination with the use of donor sperm twice during a natural or stimulated ovulation induction cycle did not increase pregnancy rates over a single insemination.


To determine whether a single or double intrauterine insemination (IUI) improves pregnancy outcomes, the authors used a retrospective cohort design in a large private practice fertility center to observe clinical pregnancy rates after a natural or stimulated cycle. A total of 3159 donor IUI cycles were studied, of which 673 single and 2486 double inseminations were performed. Only cycles utilizing donor sperm were included in the evaluation and no other exclusions were used. Prior to each insemination, frozen donor sperm was thawed and washed to remove the seminal fluid; then the supernatant was re-suspended in sterile media. A catheter containing the sperm was placed directly into the uterus, bypassing the vagina and cervix to concentrate the male gametes in an area closer to the fallopian tubes. Timing of the insemination cycle was done using a urinary test kit to detect the luteinizing hormone (LH) surge or following injection of human chorionic gonadotropin (hCG) to mimic the LH surge. The two study groups (single or double) were similar in age, body mass index, number of cycles prior to the study, chance of having diminished ovarian reserve, and type of cycle (natural vs stimulated). Whether a patient underwent a single or double insemination was up to the physician and patient. Utilizing univariate regression and generalized estimation equation modeling, multiple subanalyses were performed to observe potential differences between the methods of IUI and other factors, including patient demographics, stimulation parameters, first and multiple cycle outcomes, best prognosis patients (< 35 years of age without polycystic ovary syndrome or ovarian reserve issues), and patients with a decrease in ovarian reserve parameters. The overall clinical pregnancy rates (heartbeat noted on ultrasound in the first trimester) were not significant between the two groups: single 16.4% and double 13.6%. Also, no differences in outcome were noted during the first cycle (single 17%, double 14.4%) or in good prognosis patients (single 23.3%, double 18.9%). From a cost-effectiveness perspective, the authors noted that the cost of an extra insemination at their institution added an additional $800 to the cost of the total cycle without noted benefit.

COMMENTARY

The use of intrauterine insemination with partner or donor sperm is a useful technique for couples with unexplained and male infertility without utilizing higher cost techniques such as in vitro fertilization. Whether a single or double insemination should be performed during an individual ovulation induction cycle is a
matter of hot debate. Prior studies examining this issue have involved small numbers of subjects and have demonstrated conflicting results; double insemination was superior in two studies\(^1\,^2\) and another showed no difference between the two modalities (though the investigators of this study hypothesized double insemination superiority without significant findings).\(^3\)

The rationale for double insemination (12 and 36 hours after LH trigger) is that you place sperm in the uterus the day of and after ovulation to increase the odds that the sperm will be in the fallopian tubes at the correct time for conception. The rationale for a single insemination (36 hours after LH trigger) is that insemination is timed at or closer to ovulation, therefore increasing the chance of fertilizing the newly released egg. Our center previously demonstrated that no differences were noted with a single IUI at 24 or 36 hours after the use of hCG to trigger ovulation; therefore, sperm placed in the uterus within 12-14 hours before the egg is released does not adversely affect chances at conception.\(^4\)

The strengths of this study include the use of donor sperm as this negates the male factor as a confounding variable with these patients. It also increases the pool of patients to be studied, including single women and same-sex female couples. Though no female factor exclusions were permitted during analysis, analytic modeling techniques were used to remove a number of confounding factors and allow the investigators to observe the data many ways including first cycles, best prognosis patients, and those with a decrease in ovarian reserve. Despite these maneuvers, no differences were noted between the use of single and double insemination with donor sperm, which agrees with some of the previous data in smaller studies. Though this was the largest study to compare these two IUI treatment modalities, the authors noted weaknesses. One inherent weakness is the retrospective study design. Patients and/or physicians were allowed to choose the number of inseminations, thereby allowing three times more double inseminations over single.

This study is important for a number of reasons. First, it takes away the need for physicians to use double insemination to justify enhanced pregnancy rates. This eliminates cost for the patient already burdened with the high price of assisted reproductive technology.

Patients have a hand in pushing clinicians to do more to “increase the odds of success.” There are a plethora of patient-to-patient Internet chat rooms that give antidotal “evidence” of unheralded success rates associated with double inseminations, specific vitamins/oils/lotions from for-profit companies, alternative therapies (acupuncture, aromatherapy, relaxation tapes, etc.), and different sexual positions. Clinicians sometimes buy in to the pressure to perform more interventions from desperate, but well-meaning, patients who may threaten to go to other practices if their demands aren’t met.

This study highlights the fact that large practices are often a wealth of untapped research data. Many clinical questions can be studied since high volume is available. The ability to ask a simple question and then look at all the parameters using sophisticated modeling techniques is like moving a Rubik’s cube around to look at all the possible combinations. In this case, one important clinical question has been answered. Hopefully, double insemination will fade away.

**REFERENCES**


**ABSTRACT & COMMENTARY**

**Swedish Case-control Study Sees Increase in DVT Risk with DMPA: Is This Real?**

**By Jeffrey T. Jensen, MD, MPH**

**SYNOPSIS:** A large case-control study done in Sweden that evaluated thromboembolic complications in users of hormonal contraception found an increased risk in users of depomedroxyprogesterone acetate and the combined pill. Desogestrel-containing oral contraceptives showed an increase in risk relative to levonorgestrel pills.


The Thrombo Embolism Hormone Study was a nationwide case-control study conducted in Sweden between January 1, 2003, and March 31, 2009. Cases (n = 948) were all women with a first episode of deep
venous thrombosis (VTE) or pulmonary embolism diagnosed at 43 hospitals geographically spread throughout Sweden. The diagnosis was confirmed by imaging, and only those patients who received anticoagulation therapy were considered to be a valid case. Control subjects (n = 902) were randomly selected from the general Swedish Population Register and frequency-matched by age only. Exclusions for either group included a previous thrombosis, recent pregnancy, or current malignancy. Consenting subjects in both groups underwent a phone interview to evaluate risk factors for thrombosis including use of hormonal contraception, and were also asked to submit a blood sample to evaluate for common thrombophilias. Odds ratios (OR) were adjusted for smoking, body mass index (BMI), and immobilization.

Overall, the adjusted odds ratio (aOR) for current use of combined hormonal contraception (CHC) compared to nonusers was 5.3 (95% confidence interval [CI], 4.0-7.0). Relative to levonorgestrel (LNG) combined pills, the odds of VTE were increased for users of desogestrel (aOR, 2.6; 95% CI, 1.3-5.4) and decreased for women taking norethindrone (aOR 0.4; 95% CI, 0.2-0.9) combined pills. There was no significant difference seen with respect to LNG with drospirenone-containing pills (aOR, 2.0; 95% CI, 0.9-4.3) or the etonogestrel ring (aOR, 1.6; 95% CI, 0.4-6.1). Although there was no overall increase in VTE risk seen in users of progestin-only products (aOR, 0.9; 95% CI, 0.7-1.2), users of DMPA had a 2-fold increase (aOR, 2.2; 95% CI, 1.3-4.0). For those women who carried the factor V Leiden mutation and used a CHC, the aOR was 20.6 (95% CI, 8.9-58). The authors concluded that the increased risk of VTE associated with CHC varies by the type of progestogen and that this is independent of BMI and smoking, but further increased by thrombophilic genotypes such as factor V Leiden.

COMMENTARY

Long-time readers of OB/GYN Clinical Alert might conclude that I am obsessed with writing about VTE risk and hormonal therapy. Given that thrombosis represents the most significant risk associated with hormonal therapy, this obsession is not without merit. Also, there seems to be no end to new publications that attempt to parse out the relationship between type of progestogen and thrombosis risk. Unfortunately, in my opinion, most of what is published in this area fails to bring clarity to clinicians and frightens women away from hormonal therapy.

This most recent publication from Sweden published in the prestigious Green Journal is a big step backward. To date, the controversy has revolved primarily around the increased risk for desogestrel and drospirenone products relative to LNG observed in the quasi-prospective Danish database studies performed by Lidegaard, and the absence of association in the true prospective post-marketing studies conducted by Dinger and the ZEG institute. The passion of the debate has rocked Europe. The European Medicines Agency (EMA, a central regulatory agency similar to our FDA) issued a statement on November 21, 2013, concluding that the benefits of combined hormonal contraceptives (preventing unwanted pregnancies) outweigh their risks, and that the well-known risk of VTE with all CHCs is small and similar. In contrast, France has issued recommendations to restrict the prescription of desogestrel and drospirenone products as first-line formulations.

Since I last wrote on this topic, the long-awaited results of the International Active Surveillance Study were published in Contraception. This paper by Dinger et al described the FDA-mandated post-marketing study of the safety of the 24 day 20 mcg EE/3 mg drospirenone pill. The results (no increased risk relative to LNG) were consistent with the other studies by Dinger that showed no increase in risk with 30 mcg EE drospirenone (EURAS) or the etonogestrel ring (TASC). Strengths of these studies include the true prospective design that provides an ability to collect information on important baseline confounders such as age, family history, and BMI. Even more importantly, since these studies only enroll new starts and pill switchers, duration of use is also controlled. For readers interested in a more detailed discussion of the strengths and weaknesses of this design, a letter to the editor from Dr. Lidegaard with a critique of the INAS study and a response from Dr. Dinger are available on the journal's website.

Rather than adding clarity, the Swedish study is a big step backward. As we evaluate epidemiologic studies, the lowest level of evidence is a descriptive series. A case-control study is an improvement over a simple case series, but the inherent biases associated with selection of controls and assessment of baseline characteristics of cases and controls greatly limits the validity of conclusions. One of the primary problems with the Swedish study was the inability to control for duration of use or for other aspects of preferential prescribing. Inconsistencies are seen with respect to both the Dinger (no increase in risk with desogestrel) and Lidegaard (significant reduction in the odds ratio for VTE seen with norethindrone pills relative to LNG but no significant elevation with either etonogestrel or drospirenone) studies. The strong increase in VTE risk seen in users of DMPA is also not supported by other studies.

To summarize, the paper by Bergendal provides no new useful information on this topic. My recommendations are to approach the subject of pill prescription in terms of efficacy and safety. For many women, a long-acting reversible contraception method may be better. For women who prefer to use an oral contraceptive, most will do very well on low-cost generic pills, and these
should generally be recommended first. Some women may have baseline concerns about androgen-related side effects such as acne, and this should be taken into account during counseling. While there are insufficient data to compare various preparations head-to-head, low androgen pills may be preferable under these circumstances. Other medical problems (cyclic mood disorders, heavy bleeding) should also be considered. All combined products carry an increase in risk of VTE that is 2-3 times higher than baseline, but about half as high as the risk seen in pregnancy. Although I personally disagree with the conclusion that drospirenone and desogestrel (including the etonogestrel ring) products are associated with an increase in risk, the FDA-mandated package inserts of drospirenone pills discuss this, so it needs to be mentioned. You and your patient need to decide on her priorities and goals for prescription of a combined hormonal method. You should carefully document both the pertinent positive and negative findings on your history and exam and the clinical decision making used to choose a product. As I have mentioned previously, I think that this practice provides protection to you, and choice to your patient.

REFERENCES

SPECIAL FEATURE

Use of Cervical Length and Fetal Fibronectin in Preterm Labor

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora

Dr. Hobbins reports no financial relationships relevant to this field of study.

SYNOPSIS: A large 10-center study has validated the concept of screening all patients who are presenting with preterm contractions in the third trimester with cervical length examinations by transvaginal sonography and using fetal fibronectin selectively only in those with cervical lengths between 1.5 and 3.0 cm.


The rate of preterm birth (PTB) in the United States has dropped slightly over the last few years, but it is still unacceptably high at 11.5%. Early delivery puts significant stress not only on the affected patients and their babies but also on our obstetrical health care system. Cervical length (CL) measurements by transvaginal sonography (TVS) and fetal fibronectin (fFN) testing had been introduced as tools to predict which pregnancies are most at risk for preterm birth. However, in the last few years, studies have surfaced evaluating these tools, specifically in the third trimester, as a way to determine which patients with preterm contractions (PTC) are truly in preterm labor. Until now, most of the trials have only looked at each method independently and have had small numbers of subjects.

A group from the Netherlands recently evaluated data accumulated from 10 hospitals between 2009 and 2012. Seven hundred eight women with documented preterm contractions between 24 and 34 weeks of gestation were managed according to a single protocol, which called for fFN specimens to be initially collected from the posterior fornix followed by CL assessments by TVS. The outcome variable was delivery within 7 days of presentation.

After exclusions were applied, 702 remained in the study, of which 80 women (12%) delivered within 7 days. The median gestational age at time of entry was 29 weeks. Interestingly, in those who delivered within this window, the average time of delivery was 2.2 days after entry. Both CL and fFN were reasonably predictive of PTB < 7 days, but the two tests in combination performed better. Not surprisingly, 47% of patients with CLs < 1.5 cm delivered < 7 days. Conversely, less than 1% of the patients with CLs > 3 cm delivered < 7 days. Based on these results, the authors applied a “contingency” approach to the data that would involve performing a CL on everyone first and then using the fFN only in those whose CLs...
were in an intermediate category of 1.5-3.0 cm. With this sequential method, the chances of the 149 fFN negative patients in this intermediate category of delivering within 7 days was only 2.1%. The remaining 48 fFN positive patients in this category had a 14% chance of delivery within 7 days. This protocol would eliminate the need to admit and treat more than half of the patients (404 of the original 708) in the study, since their total risk of immediate delivery was 1.4%. The remaining 40% (which included everyone with CL < 1.5 cm and those with CL 1.5-3.0 cm who had positive fFN) would require justifiable in-hospital attention, since that group would have about a 25% risk of delivering sometime during the next 7 days.

**COMMENTS**

When walking through any antepartum service in a tertiary care hospital, one will see that the majority of the patients housed there have been labeled with the diagnosis of “preterm labor” or “arrested preterm labor.” As suggested by the above study and others, the vast majority of patients with PTC are not in true labor and, therefore, not in need of the unnecessary, and in most cases, unasked for attention that they get. Also, with this simple protocol, the expenditure of millions of dollars’ worth of hospitalizations can be averted.

The success of this simple protocol might have been anticipated from the results of an earlier study by Gomez et al. The thrust of that study was to show that the two methods (CL and fFN), used together, were more predictive of true preterm labor than CL alone. Actually, tucked within their data was similar evidence displaying the worth of using fFN selectively. Specifically, if the CL was > 3.0 cm, fFN added little to the negative predictive value. Other trials of this kind have had small numbers. This study not only had adequate numbers of patients, but also put into play a rigid protocol employed by the 10 centers, thus enabling the authors to demonstrate the usefulness of CL in all patients with preterm contractions followed by a selective use of fetal fibronectin. By inserting the swab into the posterior fornix before doing the TVS, potential contamination of the fFN specimen can be avoided. If the CL is between 1.5 and 3.0, the specimens then can be discarded.

**REFERENCES**

Clinical Briefs in Primary Care and Pharmacology Watch Available Online

The November 2014 issues of Pharmacology Watch and Clinical Briefs in Primary Care are now available exclusively by e-mail or online. You can access these two valuable supplements to OB/GYN Clinical Alert at http://www.ahcmedia.com/supplements/. We will send PDF copies of these supplements to you by e-mail if you prefer. Please send an e-mail with your name and/or subscriber number to customerservice@ahcmedia.com with Digital AHC Supplements in the subject line. We welcome your feedback and appreciate your continued support as a subscriber.

CME INSTRUCTIONS

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CME QUESTIONS

1. Women should receive the Tdap vaccine during every pregnancy in the third trimester.
   a. True
   b. False

2. A “double” intrauterine insemination is when sperm is placed in the uterus at what two standard time frames after the use of human chorionic gonadotropin (hCG) to trigger ovulation?
   a. 36 minutes and 112 minutes
   b. 30 hours and 50 hours
   c. 12 minutes and 36 minutes
   d. 12 hours and 36 hours

3. The primary conclusion of the Swedish study of hormonal contraception and VTE risk can be summarized as:
   a. The limitations of the case-control design suggest that bias may explain the finding of increased odds ratio of VTE risk seen with desogestrel combined pills and DMPA.
   b. All women of northern European background should have a screening test for the Factor V Leiden mutation before any hormonal contraception prescription.
   c. Obese women should always use a norethindrone containing 30 mcg EE pill.
   d. Desogestrel progestin-only pills have a 2-fold increase in the odds ratio of VTE compared to levonorgestrel combined pills.

4. Which patients with PTC are not at greater risk for delivery within 7 days of the initial encounter?
   a. Those with CL between 1.5 and 3.0 cm irrespective of fFN
   b. Those with CL between 1.5 and 3.0 cm with positive fFN
   c. Those with CL < 1.5 cm
   d. Those with CL between 1.5 and 3.0 cm with negative fFN

5. In the total study of patients presenting with preterm contractions, only about one in 10 patients delivered within 7 days.
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

• Explain the latest data regarding diagnosis and treatment of various diseases affecting women;

• Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and

• Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women’s health.